REMARKS

[01] Amended paragraphs for pages 1, 4, and 14 are presented in revision format as required by 37 CFR 1.121 (2). Claim 12 has been amended to correct its dependency. Claim 14 has been amended for editorial reasons. Claims 11, 15, 18, 19, 22, and 25 to clarify temporal relations.

[02] The Office Action rejects Claims 8-13, 15-23, and 25 for anticipation under 35 USC 102(e) by U.S. Patent Application Publication No. 2002/0001803 to Smith et al. This rejection is traversed as the Smith et al. does not represent "invention by another": the present Applicant is a coinventor for the Smith Application. (Applicant intends to submit a declaration under 37 CFR 1.132 stating that the invention claimed in the present application and disclosed but not claimed by Smith et al. was derived from the inventor for the present application. However, there has been delay involved in locating inventors.)

[03] Holmes' Teaching

[04] Before addressing obviousness rejections on a claim-by-claim basis, one particular argument is examined in advance for careful consideration. U.S. Patent No. 5,527,681 to Holmes, "Holmes" herein, discloses the use of centrifuging at Col. 10, lines 14-23, quoted below.

> **[05]** "In still further embodiments the reaction chamber is placed on a rotating "centrifuge" to reduce the volume of reactants needed for the various coupling/deprotection steps disclosed herein. In a centrifuge flow cell, the substrate is placed in the centrifuge such that, for example, when a monomer solution passes over the surface of the substrate a relatively thin film of the material is formed on the substrate due to the higher gravitational forces acting on the substrate. Accordingly, the volume of the various reagents needed in the synthesis will be substantially reduced."

[06] The first sentence in the quote discloses a relationship between centrifuging and volume of reactants required. The second two sentences make it clear that this relationship is not a direct one, but requires that reagent volume requirements be related to film thickness. Thus, Holmes does not teach that centrifuging will reduce reactant volume requirements in systems in which reactant volume requirements are not correlated with a film thickness.

[07] Claim 8

[08] The Office Action rejects Claim 8 as being obvious over U.S. Patent No. 5,834,758 to Trulson et al., "Trulson" herein, in view of Holmes and U.S. Patent No. 5,449,621 to Klein, "Klein" herein. This rejection is traversed.

[09] The present Office Action states that Trulson discloses centrifuging a sample fluid by rotating a reaction cell as called for by Claim 8. This assertion is made despite the fact that Trulson does not state that a sample fluid is centrifuged and does not state that a reaction cell is rotated. The Office Action erroneously attempts to equate "circulation" of a sample fluid through a reaction cell with "rotation" of the reaction cell itself. The fact that fluid circulates through a reaction cell no more implies rotation of the reaction cell that the fact that blood flowing through a human body implies the body is rotating. Applicant's traversing remarks accompanying Amendment A pointing out this error have not been rebutted. Accordingly, the Examiner should withdraw the assertion that Trulson discloses centrifuging a sample fluid and rotating a reaction cell.

[10] The present Office Action argues in the alternative that it would be obvious to modify Trulson in accordance with the teachings of Holmes to apply Holmes' centrifuging to Trulson's reaction cell. Holmes teaches that:

1) coupling reactions can take place between monomer in solution and polymer bound to a subrate;

2) the monomer solution forms a film on the substrate;

3) due to the higher gravitational forces involved, this film can be made thinner during centrifuging; and

4) since the film is thinner, the amount of monomer solution required is reduced.

[11] It would be clear to anyone skilled in the art that the reduction of volume of reagents taught by Holmes only applies where the volume of reagents is related to the thickness of a film of reagent solution. The reduction would not be achieved in cases where no film was formed or where the thickness of any film formed was not related to the volume of reagents required.

[12] In particular, the reductions achieved in Holmes' context would not be achieved in the context of the system illustrated in Trulson, Fig. 5. Trulson does not disclose that the sample fluid forms a film that could be made thinner by centrifuging. Instead, it would appear, in view of the pumping involved in agitation, that the reaction cell is full of sample solution (and any entrained agitation agents). Also, the volume of reagent in the reaction cell at any given time is only a fraction of that required by the agitation system as a whole, which includes a pair of sample fluid reservoirs and intermediate tubing.

[13] The Office Action relies on Klein for the supergravity limitation. However, Klein does not disclose agitation under supergravity conditions. Specifically, Klein discloses a centrifuge is operated at very low speeds during agitation.

[14] Since Trulson does not disclose an embodiment in which reagent volume requirements can be reduced by reducing film thickness, it would not be obvious to apply Holmes' teachings to Trulson. Accordingly, the obviousness rejection of Claim 8 is traversed.

[15] Claim 9

[16] The Office Action rejects Claim 9 as being obvious over Trulson in view of Holmes and U.S. Patent No. 4,812,294 to Combs, "Combs" herein. Claim 9 requires agitation involving rotation about an agitation axis; the agitation axis being more orthogonal than parallel to the centrifugal force resulting from centrifuging. The Office Action purports to find this limitation disclosed in Combs' abstract. However, Combs does not disclose agitation and thus does not disclose the limitation of Claim 9. Furthermore, it is apparent that Trulson's system allows fluid to flow as desired under conditions of gravity or microgravity, so there is no motivation for modifying Trulson to achieve this objective. Accordingly, the rejection of Claim 9 should be withdrawn.

[17] Claim 10

[18] The Office Action rejects Claim 10 as obvious over Trulson, Holmes, Klein, and Combs. Claim 10 depends from Claim 9 and adds the requirement that the rotational direction about the agitation axis be changed periodically. The Office Action concludes it would have been obvious to apply the direction changing of Klein to the agitation of Trulson. As noted earlier, Trulson achieves the desired agitation without rotating a reaction cell (but using direction changing) so there is no apparent benefit to modifying Trulson's system in accordance with Klein's teachings. Accordingly, the rejection of Claim 10 should be withdrawn.

[19] Claim 11

[20] Claim 11 depends from Claim 10 and adds the limitation that the centrifuge rate be greater than the agitation rate. Claim 11 has been amended to make it clear that the centrifuge rate referred to is occurs during agitating. The Office Action purports to find this limitation met in Klein, Col. 5, lines 38-44. However, this limitation cannot be found there. While the Klein discloses a maximum rotation rate of 10,000 rpm, this rate is not used in conjunction with agitation. Instead, Klein discloses that a "very low speed" rotation is used for agitation, which occurs at a rate of 3-30Hz. From the Klein Col. 5, lines 54-58, it seems that the agitation rate exceeds the rotation rate. Accordingly, the additional grounds for rejection of Claim 11 should be withdrawn.

[21] Claim 12

[22] Claim 12, as amended herein, depends from Claim 8 and adds the limitation that agitation involves rotating a reaction cell about an agitation axis that extends more parallel to than orthogonal to a centrifuge axis. The Office Action purports to find this limitation in Combs, Col. 13, lines 30-35 and Fig. 11. However, Combs does not teach a method of agitation and Trulson already achieves the desired fluid-flow for agitation without requiring the reaction-cell motions disclosed by Combs.

[23] Claim 13

[24] Claim 13 depends from Claim 12 and adds a limitation that a probe array extends more orthogonal to said centrifugal force than along it. The Office Action purports to find this limitation in Combs, but Combs does not mention a probe array. Accordingly, this additional ground for rejection of Claim 11 should be withdrawn.

[25] Claim 14

[26] Claim 14 depends from Claim 13 and adds a limitation of removing sample liquid from a reaction cell by rotating it about an agitation axis so that centrifugal force urges the fluid away from a probe array. The Office Action asserts that this limitation is found in Trulson, but Trulson does not disclose rotating a reaction cell at all, let alone so as to remove sample fluid. The Office Action attempts to equate rotating a reaction cell with agitating a fluid, but there is no basis presented for this. Accordingly, the ground of rejection should be withdrawn.

[27] Claim 15

[28] Claim 15 depends from Claim 8 and adds a limitation that the sample fluid occupies at most half the volume of a reaction cell interior. Claim 15 has been amended to make it clear that the time frame is during agitating. The Office Action asserts that Trulson discloses the "at most half full" limitation where is said "the amount of fluid in container 5010 nears empty". However, container 5010 is not a reaction cell, so the additional limitation is not disclosed by Trulson. According, the grounds for rejection pertaining to Claim 15 should be withdrawn.

[29] Claim 16

[30] Claim 16 is an independent claim. The Office Action rejects Claim 16 using reasoning roughly corresponding to the rejections of Claims 8 and 9. The Office Action erroneous determines that Trulson discloses centrifuging. The Office Action then tries to find the missing centrifuging in Holmes', but the motivation to combine falls short as discussed above. Holmes' disclosure that centrifuging can reduce reagent volume requirements is tied to situations in which the reagent volume is related to a film thickness that can be reduced by centrifuging. This condition is not met by Trulson. There is no reason to believe centrifuging would reduce reaction volume requirements in a system such as that disclosed by Trulson. The Office Action then relies on Combs for the "more orthogonal than parallel" limitation of Claim 16, but Combs does not teach the use of such orientations for the purpose of agitation. Combs purpose of guiding liquid motion through a multi-chambered reaction cell is not applicable to Trulson. Thus, Claim 16 should be allowed.

[31] Claim 17

[32] Claim 17 depends from Claim 16 and adds a limitation that agitation involves periodically changing a direction of rotation of a reaction cell, just as Claim 9 does. The traversal for Claim 9 applies here as well and the ground of rejection directed at the additional limitation of Claim 17 should be withdrawn.

[33] Claim 18

[34] Claim 18 depends from Claim 17 and adds a limitation that the rotation rate exceeds the agitation rate. Claim 18 has been amended to make it clear that the centrifuge rate is that during agitating. This limitation is analogous to that added by Claim 10 and the traversal is also analogous. The ground of rejection directed at the addition limitation of Claim 18 should be withdrawn.

[35] Claim 19

[36] Claim 19 depends from Claim 18 and adds a limitation that the interior volume of the reaction cell is at most half filled with sample fluid. Claim 19 has been amended to make it clear that the time involved is during agitating. The limitation added by Claim 19 parallels the limitation added by Claim 15 and the traversal is analogous. Accordingly, the grounds of rejection for the additional limitation of Claim 19 should be withdrawn.

[37] Claim 20

[38] Claim 20 is independent. The traversal of the outstanding rejection follows arguments presented above. Trulson does not disclose centrifuging. Holmes' teachings do not apply in a context such as Trulson in which reagent volume requirements are not correlated with film thickness. Combs does not teach anything about an agitation axis. Klein does not teach agitation under supergravity conditions.

[39] Claim 21

[40] Claim 21 depends from Claim 20 and adds a limitation regarding periodic changes in the direction of rotation of a reaction cell. Applicant agrees that it is well known for agitators to change direction. In fact, Trulson already uses changes of direction to promote agitation. However, Trulson changes the direction of pumping rather than a direction of rotation of a reaction cell. There is no reason to believe modifying Trulson in accordance with the teachings of Klein would improve upon the agitation already achieved by Trulson. Accordingly, the rejection of Claim 21 should be withdrawn.

[41] Claim 22

[42] Claim 22 depends from Claim 21 and adds a limitation that the centrifuge rate is greater than the agitation rate. Claim 22 has been amended to make it clear that the centrifuge rate is during agitation. With this clarification, it is clear that Klein does not disclose a centrifuge rate greater than the agitation rate during agitation.

[43] Claim 23

[44] Claim 23 depends from Claim 20 and adds a limitation regarding the orientation of a probe array. The Office Action purports to find this limitation disclosed in Combs. However, Combs does not disclose the presence of a probe array, hence the rejection for Claim 23 should be withdrawn.

[45] Claim 24

[46] Claim 24 depends from Claim 23 and adds a limitation regarding removal of sample fluid from a reaction cell. The Office Action purports to find this limitation in Trulson, Col. 14, lines 12-60. However, this passage describes a container other than a reaction cell that is nearly emptied. The reaction cell remains full during the time frame referred to in the cited passage. Accordingly, the rejection of Claim 24 should be withdrawn.

[47] Claim 25

[48] Claim 25 depends from Claim 20 and adds a limitation that the sample fluid occupies half the interior volume of a reaction cell. Claim 25 has been amended to make it clear that the time involved is during agitation. As with Claim 24, the Office Action confuses an agitation reservoir with the reaction cell. Trulson does not describe emptying the reaction cell itself in the cited passage.

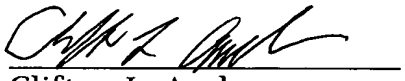
[49] Provisional Double Patenting Objections

[50] As to the two provisional double patenting rejections, Applicant is prepared to file terminal disclaimers once the provisional rejections become actual or once subject matter is held to be allowable except for the provisional double patenting rejections.

CONCLUSION

The obviousness rejections have been traversed. The rejection for anticipation is being addressed by a Declaration Under 37 CFR 1.132. The double-patenting rejections will be addressed when they become actual objections or when the claimed subject matter is held otherwise allowable.

Respectfully submitted



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Replacement paragraph for Page 1, lines 18-26 in revision format.

Hybridization reactions between surface-bound molecular probes and target molecules in a sample liquid may be used to detect the presence of particular biomaterials including biopolymers and the like. The surface-bound probes may be oligonucleotides, peptides, polypeptides, proteins, antibodies or other molecules ~~coverable~~ capable of reacting with target molecules in solution. Such reactions form the basis for many of the methods and devices used in the new field of genomics to probe nucleic acid sequences for novel genes, gene fragments, gene variants and mutations.

Replacement paragraph for Page 4, lines 3-15 in revision format.

In U.S. Patent No. 4,849,340 to Oberhardt, an alternative means is disclosed for mixing components in a fluid during an assay performed in an enclosed chamber. Oberhardt discloses an apparatus comprising a base, an overlay and a cover which when combined define a sample well, a channel, and a reaction space. Fluids introduced into the sample well flow by ~~coverillary~~ capillary action to the reaction space. Mixing of fluids within the reaction space is effected using mechanical or electromechanical means to create forced convection currents. Again, large sample volumes are required (100 to 200 μl) because of the need to maintain a gap between the base and the cover during mixing. Additionally, the method relies on ~~coverillary~~ capillary action to promote fluid flow, and mixing may thus be slow and incomplete, particularly when viscous reagents are used.

Replacement paragraph for Page 14, lines 4-23 in revision format.

As noted above, the cover preferably has a lip along the perimeter of the cover bordering a recessed portion that comprises the major portion of the area of the inner face of the cover. Applying pressure to the outer face of the cover directly above the perimeter lip is required to form the tight seal between the cover and the substrate. Any means that presses the lip of the cover securely to the substrate is suitable. Such pressure may be applied evenly by, for example, clamps, a press, or by ~~coverturing~~ capturing the substrate and cover within a two-part rigid frame and compressing the two together to supply an even pressure to the cover and substrate. If desired, the peripheral lip of the cover may be modified to provide for an improved seal; for example, one or more continuous ridges can be incorporated into the lip so that the pressure supplied to the cover is higher at those locations and preferentially causes them to compress. In any of these embodiments, the reaction cell may be re-used, as the peripheral seal is temporary and the fastening means may be removed when desired. Thus, the reaction cell may be readily disassembled after use, cleaned, and re-assembled (with alternate components, such as a different substrate, if desired) so that some or all of the components of the reaction cell may be re-used.